

## rituximab 1400mg solution for subcutaneous injection (Mabthera<sup>®</sup>)

SMC No. (975/14)

### Roche Products Limited

06 June 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**rituximab subcutaneous injection (Mabthera<sup>®</sup>)** is accepted for restricted use within NHS Scotland.

**Indication under review:** for non-Hodgkin's lymphoma (NHL) in adults:

- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy;
- treatment of patients with CD20 positive diffuse large B cell - non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

**SMC restriction:** Subcutaneous rituximab is accepted for use in line with previous SMC advice for intravenous rituximab i.e. accepted within licensed indication as above except in the maintenance setting, where use is restricted to patients who have responded to induction therapy with rituximab plus chemotherapy.

In two pharmacokinetic-based clinical bridging studies, rituximab subcutaneous injection was shown to be non inferior to rituximab intravenous infusion for trough concentration and area under the concentration time curve.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of rituximab subcutaneous injection. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Co-Vice Chairman,  
Scottish Medicines Consortium**

## Indication

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## Dosing Information

Rituximab should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. It should be administered as subcutaneous injection only, over approximately 5 minutes into the abdominal wall.

### Induction therapy

All patients must receive a full dose of rituximab by intravenous infusion (IV), using the IV formulation administered at 375 mg/m<sup>2</sup> body surface area, followed by subcutaneous injection of rituximab at a fixed dose of 1400 mg per cycle for up to 8 cycles. If patients are not able to receive one full rituximab IV infusion dose prior to the switch, they should continue the subsequent cycles with the IV formulation until a full IV dose is successfully administered.

### Maintenance therapy

In previously untreated follicular lymphoma in patients who have responded to induction treatment 1400 mg once every 2 months until disease progression or for a maximum period of two years. In relapsed/refractory follicular lymphoma in patients who have responded to induction treatment 1400 mg once every 3 months until disease progression or for a maximum period of two years.

### Diffuse large B cell non-Hodgkin's lymphoma

In combination with CHOP: first cycle, rituximab IV formulation: 375 mg/m<sup>2</sup> body surface area, followed by rituximab SC at a fixed dose of 1400 mg per cycle on day 1 of chemotherapy cycle. In total: 8 cycles. Safety and efficacy of rituximab have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

## Product availability date

23rd June 2014

## Summary of evidence on comparative efficacy

Rituximab is a monoclonal antibody that binds specifically to the antigen, CD20, located on pre-B and mature B lymphocytes and expressed on >95 % of B cell non-Hodgkin's lymphomas.<sup>1</sup>

SMC has previously accepted the intravenous (IV) formulation of rituximab for restricted use for the treatment of previously untreated patients with stage III to IV follicular lymphoma in combination with chemotherapy and for maintenance therapy in follicular lymphoma patients responding to induction therapy with rituximab in combination with chemotherapy. This submission is for a new subcutaneous (SC) formulation of rituximab, formulated with recombinant human hyaluronidase (rHuPH20), an enzyme that increases dispersion at the injection site, increasing the volume that can be administered and resulting in enhanced absorption of rituximab into the circulation.<sup>1,2</sup>

The evidence to support the use of rituximab SC as an alternative to rituximab IV is primarily based on the SABRINA study. This was a phase III, randomised, non-inferiority, open-label study conducted in two stages in patients with previously untreated, histologically confirmed, CD20-positive grade 1, 2 or 3a follicular lymphoma who were  $\geq 18$  years, with Eastern Cooperative Oncology Group performance status of 0 to 2, and bi-dimensionally measured disease.<sup>2</sup> Patients with transformation to high-grade non-follicular lymphoma, or malignancies other than follicular lymphoma were excluded. In stage 1 of the study, induction treatment with rituximab in combination with chemotherapy, 127 patients were randomised equally to 375mg/m<sup>2</sup> body surface area (BSA) of IV rituximab once every 3 weeks for 8 cycles or 375mg/m<sup>2</sup> BSA of IV rituximab once in cycle 1 followed by SC rituximab at a fixed dose of 1400mg once every 3 weeks for cycles 2 to 8. Randomisation was stratified by Follicular Lymphoma International Prognostic Index (FLIPI) score, chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine, prednisolone [CHOP] or cyclophosphamide, vincristine, prednisolone [CVP]) and region. The chemotherapy regimen used in combination was chosen by the treating physician. All responders entered stage 2 of the study which assessed maintenance treatment with rituximab IV or SC administered once every 8 weeks for up to 2 years.

The primary outcome for stage 1 of the study was the rituximab trough concentration ( $C_{\text{trough}}$ ) level at induction cycle 7 (prior to cycle 8 dose) measured in the per protocol (PP) population. The  $C_{\text{trough}}$  geometric mean was higher in the SC group (134.6 microgram/mL, n=48) than in the IV group (83.1 micrograms/mL, n=54) giving an SC: IV ratio of 1.62 (90% confidence interval [CI]: 1.36 to 1.94). Since the lower limit for the two-sided 90% CI of the SC: IV geometric mean ratio exceeded the pre-specified margin of 0.8, non-inferiority was demonstrated. The coefficients of variation for  $C_{\text{trough}}$  at cycle 7 were similar in both groups: 43% in the SC group and 37% in the IV group. Of the 25 patients not included in the PP analysis, 14 had missing  $C_{\text{trough}}$  data and 11 had their samples taken outwith the predefined time window. The chemotherapy regimens used in combination with rituximab were similar in both groups, with 63% of patients receiving CHOP and around 37% receiving CVP chemotherapy.

Secondary outcomes included the geometric mean for area under the concentration time curve (AUC) at cycle 7 which was higher in the SC group (3779 microgram.day/mL) compared with the IV group (2734 microgram.day/mL), giving a geometric mean ratio of AUC SC:IV of 1.38 (90% CI: 1.24 to 1.53). Overall response rate (ORR), defined as patients who achieved a complete response, unconfirmed complete response, or partial response at the end of induction treatment was achieved by 90% and 84% of patients in SC and IV groups when assessed by investigators and 86% and 88%, respectively, when assessed by independent review.

Stage 2 of the study assessing safety and efficacy of maintenance treatment in responders from stage 1 plus an additional 280 patients is ongoing and results are awaited.

Supporting evidence comes from the SparkThera study, a 2-stage phase 1b study of rituximab SC versus rituximab IV maintenance treatment in 154 adult patients with first-line or relapsed follicular lymphoma (grade 1, 2 or 3a), who had responded to rituximab induction therapy.<sup>3</sup> Stage 1 used model-based simulations to predict a fixed dose of rituximab SC 1400 mg for use in stage 2. In stage 2, all patients received one dose of rituximab IV 375mg/m<sup>2</sup> maintenance then were randomised to rituximab SC 1400mg or rituximab IV 375mg/m<sup>2</sup> on day 1 of each cycle for their remaining maintenance cycles, stratified by the frequency of maintenance dosing (every 2 or every 3 months) for up to 2 years. The primary outcome was the geometric mean  $C_{\text{trough}}$  values for rituximab SC versus IV. The geometric mean ratios for  $C_{\text{trough}}$  SC: IV were 1.24 and 1.12, for 2 and 3 monthly administration, respectively. As the lower limits of the 2-sided 90% CI, 1.02 for 2 monthly and 0.86 for 3 monthly administration exceeded the protocol-specified non-inferiority limit of 0.8, non inferiority was demonstrated. The geometric mean AUC SC: IV ratio was 1.35 for both 2 and 3 monthly administration, and the lower limit of the 2-sided 90% CI was 1.23. Median treatment duration was 14.8 months in the SC group and 13.8 months in the IV group.

## Summary of evidence on comparative safety

No new safety concerns have been identified with this new formulation, although there were significantly higher administration-related reactions reported for subcutaneous administration.<sup>2</sup>

In the SABRINA study<sup>2</sup>, after a median follow-up of 8.8 months in the SC group and 8.7 months in the IV group, adverse events were reported in 92% (57/62) and 88% (57/65) of patients, respectively. The most frequently reported adverse events were neutropenia, nausea and constipation. Treatment-related adverse events were reported in 73% (45/62) and 46% (30/65) of patients respectively. The number of patients with serious adverse events did not differ between groups (23% and 22% respectively).

The most common reason for interruption to rituximab dosing was infusion-related adverse events and occurred in cycle 1. Administration-related reactions were reported in 32% of patients receiving IV rituximab compared with 50% of patients receiving SC rituximab: the majority of these were of grade 1 or 2 severity. One patient had a grade 3 administration-related reaction (vomiting) in the IV group, and three patients in the SC group (injection-site rash after first SC administration, dry mouth after first SC administration, decreased urine output and tumour lysis syndrome after initial IV infusion); none of these events led to treatment discontinuation. No grade 4 administration-related reactions occurred. Three patients in each group discontinued treatment.

The immunogenicity profile was similar in both groups. Two patients in each group had a positive human antichimeric antibodies result after baseline but this did not affect the adverse event profile in these patients. No patients tested positive for neutralising anti-rHuPH20 antibody.

In the SparkThera study<sup>3</sup>, rituximab SC was generally well tolerated with an overall adverse event profile similar to IV administration. Local treatment related adverse events were more frequent in the SC group, reflecting the method of administration. However, the majority of events were mild and reversible.

## Summary of clinical effectiveness issues

Rituximab is an established medicine for follicular lymphoma, which has previously been administered via IV infusion (10mg/mL) that can last for between 90 minutes and 6 hours with the dosage based on BSA calculations. This new SC formulation of rituximab has a concentration of 120mg/ml and is given as a fixed dose of 1400mg over approximately 5 minutes. Not all indications for rituximab IV are licensed for the SC formulation.

The clinical development programme for rituximab SC was based on a pharmacokinetic-based clinical bridging study demonstrating non-inferiority in pharmacokinetic outcomes and similarity in clinical response for SC versus IV rituximab. As the pharmacokinetic parameters of  $C_{trough}$  and AUC levels are generally accepted to correlate with efficacy, by demonstrating pharmacokinetic non-inferiority of these parameters with the recommended IV rituximab dose, similar efficacy was assumed. This has been demonstrated in the SABRINA<sup>2</sup> for induction and the SparkThera<sup>3</sup> study provides evidence for maintenance dosing.

There are some limitations in the evidence base. In the phase III, SABRINA study, stage 2 assessing the maintenance phase of treatment is ongoing. Patient numbers in stage 1 of the SABRINA study

were small (n=127)The evidence base is dependent on pharmacokinetic data and more supporting clinical outcomes are awaited.

The adverse event profile was similar for both formulations although as would be expected more patients experienced injection site reactions in the SC group but the majority have been of grade 1 or 2 severity.

This new formulation offers advantages to the patient and service in terms of reducing the administration time to approximately 5 minutes. The single fixed-dose of 1400mg for all patients removes the risk of errors in dosing based on BSA calculations. However it should be noted that rituximab SC is limited to use in second or subsequent cycles after an initial dose of IV rituximab.

Experts contacted by SMC advise that this new formulation offers significant advantages in convenience for the patient in terms of infusion time which should be advantageous particularly in the maintenance setting and to the service in terms of nursing time and bed/chair time which should facilitate throughput of patients.

## Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis (CMA) comparing rituximab SC with rituximab IV for the treatment of previously untreated patients with stage III-IV follicular lymphoma, follicular lymphoma patients responding to induction therapy, and for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP. Both the medicine and the comparator are used in combination with two chemotherapy regimens CHOP or CVP. The analysis was carried out from an NHS Scotland perspective and based on a one year time horizon. The comparator within the analysis contains the same active ingredient as the intervention, with the only difference between them being the method of administration. The comparator is appropriate.

The CMA was underpinned by the data from the pivotal study, which demonstrated non-inferiority of rituximab SC to rituximab IV. The economic analysis therefore focussed on the relative costs per patient for rituximab SC versus rituximab IV. The analysis took into account the respective medicine costs and also the non-medicine costs associated with, for example, administration and preparation. Rituximab IV dose is based on BSA, and the submitting company used the Systemic Anti-cancer Therapy (SACT) database to calculate the medicine costs associated with rituximab IV. Rituximab SC is a fixed dose and therefore is independent of body weight.

The base case results for a full course treatment for the overall analysis (medicine and non-medicine costs) were incremental costs per patient of £78 with rituximab SC. This was comprised of incremental medicine costs per patient of £860 and non-medicine savings per patient of £782.

A patient access scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered which reduced the list price of the medicine. With the PAS rituximab SC became a cost-effective treatment option.

The company has submitted a robust economic case, with savings demonstrated for SC in terms of both medicine and non-medicine costs. The only minor uncertainty surrounds the savings associated with patients who may have low BSAs. The average BSA for the full patient population was 1.86m<sup>2</sup>, but an analysis of female patients alone (mean BSA of 1.73m<sup>2</sup>), indicated that although there would be incremental medicine costs associated with rituximab SC, the non-drug savings would offset the incremental drug costs. Therefore, this analysis did not affect the overall conclusions

In summary, the economic case for rituximab SC has been demonstrated.

Other data were also assessed but remain commercially confidential.\*

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

In January 2012, the National Institute for Health and Care Excellence (NICE) multiple technology appraisal No 243<sup>4</sup>: Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of NICE technology appraisal guidance 110)

This guidance states that rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP),
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP),
- mitoxantrone, chlorambucil and prednisolone (MCP),
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- $\alpha$  (CHVPi), or chlorambucil,

is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.

In December 2011 the British Committee for Standards in Haematology (BCSH)<sup>5</sup> published “Guidelines on the investigation and management of follicular lymphoma” in which they recommended that rituximab in combination with chemotherapy should be used in patients with newly diagnosed, symptomatic advanced stage follicular lymphoma. There is currently no strong evidence to support one chemotherapy regimen over another. Rituximab maintenance after successful induction therapy prolongs progression-free survival and is recommended in patients responding to first-line rituximab based chemotherapy.

## Additional information: comparators

IV rituximab

## Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
Rituximab subcutaneous injection	1400mg once per cycle cycles	1345
Rituximab intravenous injection	375 mg/m <sup>2</sup> body surface area once per cycle	1222

All patients receive an initial intravenous infusion of 375mg/m<sup>2</sup>. Body surface area based on 1.8m<sup>2</sup>. Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS on 8.4.14.

## **Additional information: budget impact**

### Without PAS

The submitting company estimated the population eligible for treatment to be 661 patients in year 1 and in year 5, with an estimated uptake of 100% in all 5 years.

The gross impact on the medicines budget was estimated to be £6.67m in year 1 and in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £568k in year 1 and in year 5.

The non-drug impact on the budget was estimated to be savings of £517k in year 1 and in year 5. The overall budget impact was estimated to be a cost of £51k in year 1 and in year 5.

*Other data were also assessed but remain commercially confidential.\**

## References

The undernoted references were supplied with the submission.

1. MabThera® Summary of Product Characteristics. Roche Products Ltd
2. Davies A, Merli F, Mihaljevic B et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study *Lancet Oncol* 2014;15:343-352
3. Salar A, Avivi I, Larouche J-F et al. Final results of the BP22333 study demonstrate non-inferior pharmacokinetics and safety of subcutaneous administration of rituximab compared with intravenous administration as maintenance therapy in patients with follicular lymphoma. American Society of Haematology (ASH) Meeting, Dec 2012: Abstract 1641
4. National Institute for Health and Care Excellence Technology Appraisal No. 243, 2012, 'Rituximab for the first-line treatment of stage III-IV follicular lymphoma: (review of NICE technology appraisal guidance 110), January 2012.
5. McNamara C, Davies J, Dyer M et al. Guidelines on the Investigation and Management of Follicular Lymphoma: *British Journal of Haematology* 2011;156:446-467

This assessment is based on data submitted by the applicant company up to and including 15 April 2014.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_Statements/Policy\\_Statements](http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements)*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.



**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*